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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Examiner	:	C. Tsang
Group Art Unit	:	1202
Applicants	:	Coates et al
Serial No:	:	07/835,964
Filed	:	February 20, 1992
Assignee	:	BioChem Pharma, Inc.
For	:	1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES

New York, New York
January 23, 1997

Hon. Assistant Commissioner
For Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

Pursuant to 37 C.F.R. § 1.192 and the Examiner's August 19, 1996 Advisory Action, applicants file this Appeal Brief, in triplicate. A Notice of Appeal in this case was filed on July 19, 1996.

In view of the arguments and authorities set forth below, this Board should find the final rejection of claims 3-5, 7, 10, 21 and 22 of this application to be in error. That final rejection should be reversed.

Concurrently herewith, applicants submit a Petition For Extension Of Time Pursuant To 37 C.F.R. § 1.136(a) requesting an extension of 4 months in which to submit this appeal brief. The requisite fee under 37 C.F.R. § 1.17(d) also is enclosed. With such petition and fee, this appeal brief is

due on or before January 23, 1997, and thus, is timely. 37 C.F.R. § 1.191(d).

Pursuant to 37 C.F.R. § 1.17(f), applicants enclose herewith a check in the amount of $300.00 in payment of the filing fee for this Appeal Brief. Applicants also request an oral hearing before the Board of Patent Appeals and Interferences. Applicants previously submitted with their July 19, 1996 Notice of Appeal a check in the amount of $540.00 in payment of the fee required for filing a Notice of Appeal and a request for oral hearing under 37 C.F.R. § 1.17(e) and § 1.17(g).

The Assistant Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to Deposit Account No. 06-1075. A duplicate copy of this authorization is enclosed.

This brief has the following Appendices:

Appendix A - Pending claims 3-5, 7, 10, 21-23 of the application.

Appendix B - Application Serial No. 07/835,964, filed February 20, 1992.

Appendix C - Final Rejection, dated January 19, 1996.

Appendix D - Advisory Action, dated August 19, 1996.

Appendix E - U.S. Patent No. 5,047,407, granted September 10, 1991.

Appendix F - European Patent No. EP-382,526, published May 15, 1996.

Appendix G - E. De Clercq, "HIV Inhibitors Targeted at the Reverse Transcriptase," AIDS Research and Human Retroviruses, 8, pp. 119-143 (1992).

Appendix H - Scientific references cited herein.

Appendix I - Declarations

Appendix J - U.S. Patent Application No. 08/460,854 Claims

Appendix K - U.S. Patent Application No. 08/464,583 Claims

REAL PARTY IN INTEREST

This application is assigned to BioChem Pharma Inc, 275 Armand Frappier Boulevard, Laval, Quebec, CANADA H7V 4A7.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to appellants' legal representatives or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Assignee, however, draws the Board's attention to co-pending United States patent application 08/460,854, filed June 5, 1995. That application is a continuation of the instant application. The claims of the continuation application comprise identical subject matter to claims 3-5, 7, 10, 21 and 22 of the instant application and antiviral active metabolites or residues thereof.*

Methods for the preparation of a compound of this invention are also the subject matter of pending claims 4-5, 12, 16-18 of United States divisional application 08/464,583. That application also claims priority from the instant application.*

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* Assignee has attached as Appendix J and K, respectively, a copy of claims pending in the continuation and divisional applications.

To resolve any "same invention" double patenting issues, assignee will abandon either this case, or the same claims in the continuation application, as appropriate, upon allowance of the claims in the other case. To overcome any "obviousness-type double patenting" issues, applicants will file terminal disclaimers, as necessary, at the appropriate time.

STATUS OF THE CLAIMS

Claims 3-5, 7, 10, 21 and 22 of this application, set forth in Appendix A, are the subject of this appeal. All of these claims have been finally rejected under 35 U.S.C. § 102 and § 103 as unpatentable over European patent publication EP-382,526 (the EP '526 application) and U.S. Patent 5,047,407 (the '407 patent).

Claims 1-2, 6, 8, 9, and 11-20 have been cancelled.

STATUS OF AMENDMENT AFTER FINAL REJECTION

Assignee's Amendment pursuant to 37 C.F.R. § 1.116 and Response to Final Office Action filed July 19, 1996 sought to amend claims 7 and 10 and add claim 23. That Amendment was not entered (See Appendix D).

SUMMARY OF THE INVENTION

The present invention is directed to the (-)-enantiomer of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one in substantially pure form (Appendix B, Figure I-1 on page 1, lines 37-49; page 2, lines 7-24; and page 2, lines 25-30) and a pharmaceutically acceptable salt,

ester, or salt of ester (page 2, line 32 to page 3, line 44 and page 12, lines 22 to 54).

The present invention also provides for pharmaceutical compositions comprising a compound of this invention and a pharmaceutically acceptable carrier (page 5, line 47 to page 8, line 16).

Finally, the present invention is directed to the use of a compound of this invention in the treatment of a viral infection in a mammal (page 4, line 9 to 14, lines 23 to 37, and page 4, line 43 to page 5, line 34).

ISSUES FOR REVIEW

There are two issues for review in this appeal:

(1) Whether, under 35 U.S.C. § 102, BioChem Pharma's prior disclosures (the '407 patent and the EP '526 application) anticipate claims to a specific optical isomer (i.e. the (-)-enantiomer), which has unexpected and surprising properties, and claims to a method of treatment using that isomer;

(2) Whether, under 35 U.S.C. § 103, the claimed (-)-enantiomer, which has unexpected and surprising properties, would have been obvious to a person of ordinary skill in the art at the May 2, 1990 priority date of the application.

GROUPING OF CLAIMS

All of claims 3-5, 7, 10, 21 and 22 stand or fall together on each of the appealed issues.

ARGUMENTS

BioChem Pharma previously described and claimed a new class of nucleoside analogues, i.e., 1,3-oxathiolane nucleoside

analogues, including 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, its geometric isomers, its optical isomers, and mixtures of those isomers (Appendix E, claim 10). See the '407 patent and the EP '526 application. In that patent and application, BioChem Pharma also specifically exemplified the synthesis of cis-2-hydroxymethyl-5-(cytosin-1'yl)-1,3-oxathiolane ("compound Cis XI" in the '407 patent), also known as "BCH-189", containing the (-)-enantiomer and (+)-enantiomer of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and demonstrated that Cis XI had antiviral activity and low toxicity (col 7, line 57 - col 8, line 2; Table 1).*

In this application, BioChem Pharma has claimed a new and improved oxathiolane nucleoside -- the substantially pure (-)-enantiomer of the prior racemic mixture, Cis XI. That enantiomer, as demonstrated for the first time in the May 2, 1990 priority application, has unexpected and surprising properties. It is equipotent to the (+)-enantiomer and has a lower cytotoxicity. This results in a much improved therapeutic index.

As described in more detail below, the activity and low toxicity of the claimed (-)-enantiomer was surprising and unexpected. At the May 2, 1990 priority date of this application, the skilled worker believed that the natural or D enantiomer of nucleoside analogues (here the (+)-enantiomer) would be active and that the unnatural or L enantiomer (here the (-)-enantiomer) would be inactive or have a substantially reduced activity. It was also believed that toxicity followed

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* Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane and cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one are different names for the same compound.

activity. Yet, contrary to those expectations, the claimed (-)-enantiomer is both equipotent to the (+)-enantiomer and much less cytotoxic than the (+)-enantiomer.

The Examiner has rejected the pending claims under § 102 and § 103 over the '407 patent and the EP '526 application. Those rejections are in error and should be reversed.

I. EP 382,526 Is Not Prior Art

EP 382,526 was published on August 16, 1990, more than three months after the May 2, 1990 priority date of this application. As such, it is not "prior" to this application.

This application claims priority from Great Britain application GB 9009861.7. That priority application is identical in its disclosure to the present application. A certified copy of the priority document was timely filed under the Patent Cooperation Treaty during the international stage of this application. No further documentation is necessary to perfect applicants' priority claim.

Accordingly, the EP '526 application is not prior art to the claims of this application and the §§ 102 and 103 rejections with respect to this application should be reversed.

II. The (-)-Enantiomer Is Not Anticipated by the Racemate

The Examiner contends that claims to the (-)-enantiomer of BCH-189 are anticipated by the '407 patent, which discloses 2-hydroxymethyl-5-(cytosin-1'yl)-1,3-oxathiolane, its geometric isomers, its optical isomers and mixtures of those isomers. The Examiner has refused to acknowledge that the special and unexpected properties of the

(-)-enantiomer of BCH-189 render it patentable over the '407 patent.

Selection inventions have long been held to be patentable. Selection patents or improvement patents promote and protect inventions that significantly improve upon the original. Thus, although a species may infringe another patent because they fall within a claimed genus of that patent, the species may nevertheless represent patentable subject matter provided that it possess surprising and unexpected properties (See In re Rohm, 462 F.Supp. at 733, 201 USPQ at 81; In re Kaplan, 789 F.2d 1574, 229 USPQ 678 (Fed.Cir. 1986); In re Baird, 16 F.3d 380, 29 USPQ 1550 (Fed.Cir. 1994); In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed.Cir. 1992)). This is black letter law which the Examiner refuses to accept.

Courts have also routinely held that a compound having unexpected or surprising activity is patentable over a mixture containing that compound. In particular, claims to an enantiomer with unexpected properties "substantially free" of another enantiomer is patentable even when methods of separation of those enantiomers are known in the prior art. See, e.g., Application of Williams, 171 F.2d 319, 80 USPQ 150 (CCPA 1948); Sterling Drug v. Watson, 135 F.Supp. 173, 108 USPQ 37 (D.D.C. 1955) (the District Court reversed Board's decision based on the unexpected therapeutic properties of the claimed enantiomer); Application of May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (CCPA considered novel an enantiomerically enriched benzomorphan analgesic whose racemic counterparts were known analgesics and whose properties were unexpected).

These decisions set forth the standards under which the patentability of single enantiomers must be judged. The

standard is one of unexpected or surprising activity compared to the racemate. That the corresponding racemate was known is irrelevant so long as the claimed enantiomer possesses surprising beneficial properties. It is also irrelevant that the separation of the enantiomers was within the skill of the art. Rather, these cases turn upon the discovery of the unexpected properties of the claimed compounds.

The Examiner has ignored the point of these cases. The (-)-enantiomer is patentable as a selection invention over disclosure of the '407 patent.

One of skill in the art would not have expected and would not have chosen the claimed (-)-enantiomer prior to applicants' disclosure of its superior therapeutic index (see arguments below). Therefore, based on the case law, applicants' disclosure of the racemic mixture, Cis XI, and its individual optical isomers should not preclude their right to claim the (-)-enantiomer. They were the first to disclose that enantiomer's surprising and unexpected properties.

III. The "Choice" of the Non-Natural or L-Enantiomer

The Examiner asserts that the number of compounds disclosed in the '407 patent (i.e. the four geometric and optical isomers) is "sufficiently small to support a 102 rejection."

The Examiner cites two cases to support her view, In re Sivaramakrishnan, 213 USPQ 441, and In re Schaumann, 197 USPQ 5. Each can be distinguished from the present case on its facts. In Sivaramakrishnan, the subject matter in dispute was expressly recited in the prior art document. No such disclosure is present here. There is no disclosure in the '407 patent

which expressly points to the (-)-enantiomer. In Schaumann, the Court held that the "small" group of compounds had common properties. Here, the (-)-enantiomer has uncommon, unexpected and special properties. These cases are, thus, inapposite and do not support the Examiner's rejection. It should be reversed.

As evidenced below, those of skill in the art on the May 2, 1990 priority date of this application, with the '407 patent in hand, would not have been motivated to choose the presently claimed (-)-enantiomer. This particular enantiomer would not have been expected to possess significant antiviral activity and even if it was, it would not have been expected to have such low cytotoxicity.

Contrary to the Examiner's opinion, administration of the racemic mixture is not equivalent to administering the substantially pure (-)-enantiomer. The experts have agreed that the administration of the racemate is unlikely to provide soley the (-)-enantiomer (see Appendix I, Declarations of Drs. Mark Wainberg and Leroy Townsend).

Rather, BioChem Pharma has provided uncontroverted evidence that the discovery of the potency and low toxicity of the non-natural or L enantiomer of Cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one was a total departure from the knowledge and skill of the art at the priority date of this application (See below). At that date, the skilled worker would have expected and predicted that the "natural" or D enantiomer possessed the desired antiviral activity and that the non-natural or L enantiomer would be either devoid of activity, or have substantially reduced activity. In the case of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one, the natural D enantiomer

is the (+)-enantiomer and the non-natural or L enantiomer is the (-)-enantiomer.

The Declaration of Dr. Storer demonstrates that one of skill in the art would not have been motivated to evaluate the (-)-enantiomer of cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane (see Appendix I). The Declarations of Dr. Mark Wainberg and Dr. Leroy Townsend, each having extensive experience in the study of nucleoside analogs, establish that prior to the priority date of the application, those of skill in the art would have expected that the (+)-enantiomer would be active and the "nonnatural" or (-)-enantiomer relatively inactive.

Specifically, the Declarations of Drs. Wainberg and Townsend provided the following evidence:

1. In May 1990, those of skill in the art would have expected *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one to behave as other nucleoside analogs, irrespective of whether and how it differs from AZT, DDI and DDC.

2. In May 1990, those of skill in the art expected antiviral activity of nucleoside analogs to reside in the enantiomer most closely resembling the natural or D nucleoside. The non-natural or L enantiomer was expected to possess little or no antiviral activity. The skilled worker was, thus, surprised when BioChem Pharma reported that the non-natural or (-)-enantiomer of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one was equipotent to the natural or (+)-enantiomer.

3. In May 1990, those of skill in the art believed that antiviral activity and cytotoxicity went hand in hand and thus would not have expected a difference in cytotoxicity between the equipotent (+) and (-)-enantiomers of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one.

4. Those of skill in the art were surprised by and could not have predicted the superior properties exhibited by the claimed (-)-enantiomer.

As a consequence of those special properties of the claimed invention, applicants have given the public a markedly improved antiviral drug. At least three articles published after the filing date of this application confirm the novelty of this invention and the unexpectedness of these properties (See Appendix H).

(1) Beach et al., Synthesis of Enantiomerically Pure (2'R,5'S)-(-)-1-[2-(Hydroxymethyl) oxathiolan-5-yl]cytosine As A Potent Antiviral Agent Against Hepatitis B Virus (HBV) And Human Immunodeficiency Virus (HIV)", J. Org. Chem., 57, pp. 2217-2219 (1992).

Beach states that "the β-D-isomer of nucleosides are in general the biologically active isomers" (page 2217, column 1) but concludes that "(2'R, 5'S)-(-)-Cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one 3 [the non-natural or L enantiomer] [is] more potent than (2'S, 5'R)-(+)-BCH-189 2 [the natural or D enantiomer] by at least one order of magnitude. The significance of this finding is the fact that this is the first example of an L-like nucleoside

found to be more potent than a D-like nucleoside" (page 2219, column 2).

(2) Chang et al., "Deoxycytidine Deaminase-Resistant Stereoisomer Is The Active Form of (±)-2',3'-Dideoxy-3'-Thiacytidine In the Inhibition of Hepatitis B Virus Replication", J. Biol. Chem., 267, pp. 13938-13942 (1992).

Chang independently studied the antiviral activities of 1,3-oxathiolane nucleoside analogues of this invention. Chang acknowledged that "[i]t has always been assumed that the active stereoisomer of these analogs would be the one which most closely mimicked the natural nucleoside" (page 13941, column 2). Chang also confirmed that the compound of this invention "is the first nucleoside analog with the unnatural sugar configuration demonstrated to have antiviral activity" (Abstract, page 13938).

(3) Schinazi et al., "Activities of The Four Optical Isomers of 2',3'-Dideoxy-3'-Thiacytidine (BCH-189) Against Human Immunodeficiency Virus Type 1 in Human Lymphocytes", Antimicrobial Agents And Chemotherapy, 36(3), pp. 672-676 (1992).

Schinazi states "[t]he unexpected finding that certain L isomers of nucleoside analogs of BCH-189 are potent and selective antiviral agents opens new approaches for the treatment of viral infections with nucleosides with the unusual L conformation [sic]."

For these reasons alone, the claimed non-natural or (-)-enantiomer of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-

5-yl)-(1H)-pyrimidin-2-one is inventive over the '407 patent and the Examiner's rejection should be reversed.

IV. The Surprising and Unexpected Activity and Low Toxicity of the Non-Natural (-)-Enantiomer

The non-natural (-)-enantiomer of this invention has an unusual and surprising combination of activity and low toxicity. First, the claimed (-)-enantiomer unexpectedly has about the same activity as the natural (+)-enantiomer (page 28, Table 1 and 2). As discussed above, this was totally unknown. Second, and more importantly, the claimed (-)-enantiomer is much less toxic than the natural (+)-enantiomer. Table 3, on page 29 of the specification, for example, demonstrates that the (-)-enantiomer of this invention is as much as 100 times less toxic than the corresponding (+)-enantiomer and up to 30 times less toxic than the corresponding racemate. This demonstrates that the "non-natural" enantiomers of this invention are not only unexpectedly active, but surprisingly nontoxic.

Good activity and low toxicity (corresponding to a high therapeutic index) are essential for an effective therapeutic agent. As such, the claimed (-)-enantiomer or 3TC™ has significantly contributed to HIV therapy and the study of antiviral nucleosides in general (see page 675, lines 35-39, e.g., Schinazi, supra). Applicants have, as a result, provided the public for the first time with an unexpectedly superior compound for use in the treatment of viral infections.

V. De Clercq Does Not Suggest The Unexpected Properties of the Claimed (-)-Enantiomer

In her Final Official Action, the Examiner attempted to show that the special properties of the (-)-enantiomer were

disclosed by E. De Clercq, "HIV Inhibitors Targeted at the Reverse Transcriptase," AIDS Research and Human Retroviruses, 8, pp. 119-143 ("De Clercq") (See Appendix G). The Examiner's reliance on De Clercq is flawed for three reasons.

First, De Clercq was published in 1992, two years after the effective filing date of this application. Thus, nothing in De Clercq represents what was known or believed by those of skill in the art at applicants' filing date.

Second, the Examiner states that "(-)carbovir is as active as (+)carbovir but is significantly less toxic." This is false. The De Clercq article makes no reference whatsoever to (+) carbovir's activity or toxicity. Only the (-) carbovir and the racemate were tested. Furthermore, (-)-carbovir is the natural or D-configuration of that nucleoside analogue. Thus, De Clercq supports, rather than contradicts, BioChem Pharma's evidence that the non-natural (-)-enantiomer has surprising and unexpected properties.

Third, Examiner erroneously attempts to compare the cytotoxicity of the racemate and (-)carbovir using De Clercq's assembly of data from two different articles with studies from two different cell lines (see page 122, Table 1 citing prior publications pertaining to (-) carbovir and (±) carbovir (i.e., the racemate)). Even the same compound demonstrates very different antiviral activity and toxicity values in different cell lines. See, e.g., Vince and Brownell's* comparison of the antiviral activity and toxicity of (+) and (-) carbovir in MT-2C cells and H9 cells:

> "(-)-Carbovir showed an EC_{50} at 0.32 μg/mL (antiviral effect) while the cell viability profile of the MT-2C cells incubated with increasing concentrations of compound

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* Cited in De Clercq (copy enclosed).

revealed and IC_{50} (cytotoxic effect) at 135 µg/mL. Thus, (-) carbovir exhibited a therapeutic index of 422 in this assay system. Conversely, the (+) isomer of carbovir is relatively inactive with an EC_{50} >50µg/mL" (p. 914)

and

[In H9 cells] (-) Carbovir showed and EC_{50} at 0.8 µM compared to >60µM for (+) carbovir.... Evaluation of the carbovir enantiomers in uninfected H9 cells revealed IC_{50} values of >2mM (the highest concentration tested)" (p. 915). [Therapeutic index of (-) carbovir = 2500.]

As such, a comparison of the activity and cytotoxicity of the racemate and (-) carbovir based on De Clercq is not possible.

Interestingly, (-)carbovir like the (-)-enantiomer of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one has a substitution in the ring of the sugar. The Examiner likens (-)carbovir to other natural nucleosides or nucleoside analogues in order to compare its activity to (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. In doing so, the Examiner refutes her own assertion that the surprising activity of (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one cannot be compared to other natural nucleosides.

Thus, the Examiner's characterization of the data provided in De Clercq does not refute BioChem Pharma's evidence. It supports it.

VI. "Obvious to Test" Is Not The Proper Standard

The Examiner finally argues that it would be "routine" to test all possible stereoisomers of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one.

The Examiner erroneously points to Chang et al. (see Appendix H), which describes the four enantiomers of 2-hydroxy-

5-(cytosin-1'-yl)-1,3-oxathiolane. She concludes that one of skill in the art would routinely test all possible stereoisomers. The Examiner is in error on several accounts including the test for obviousness.

First, Chang et al. was published after the priority date of this application and after the publication of the PCT counterpart of this application. Therefore, Chang et al. is not prior art.

Second, the test for obviousness is whether the process to be carried out would have a reasonable likelihood of success viewed in the light of the prior art at the relevant date. Applicants have already cited a number of articles and declarations from experts indicating that one of skill in the art would not be motivated to test all four geometric and optical isomers at the priority date. At that date, prior nucleotide analogues studies would have favored the natural analogue.

The test for obviousness also requires that the full field of the invention be considered "including that which might lead away from the claimed invention." In re Dow Chemical Co., 837 F.2d. 469, 473, 5 USPQ 2d 1529, 1531-32. Thus, the state of the art at the priority date of this application -- the natural or D enantiomer was presumed the active enantiomer -- actually teaches away from the claimed invention.

VII. The Use of the (-)-Enantiomer in Treating Viral Diseases

The Examiner has objected to the language "treatment of a mammal . . . susceptible to viral infection" in claim 10 under 35 U.S.C. § 112 as confusing. The Examiner has suggested that alternative language "A method of treatment of AIDS..." is

commensurate with the scope of the evidence provided and urged by applicants. Applicants traverse.

Applicants have stated that compounds of this invention are useful for the treatment of viral infections, in addition to HIV. Applicants have provided information about suitable dosage ranges (page 5), toxicity (page 29), route of administration (pages 5-8), pharmaceutical formulations (pages 5-8, and Examples 6-9), combination therapies (pages 8-9), and biological activity (pages 27-29). Based on this disclosure, one of skill in the art of clinical medicine would certainly know how to use the claimed compounds for the treating HIV and other viral infections.

The Declaration of Dr. Hugh McDade establishes that fact (See Appendix I). In his declaration, Dr. McDade demonstrates that one of skill in the art would "know how to use" the claimed invention "to treat viral infections."

Furthermore, applicants have now conducted phase I, II, and III Clinical Trials of the claimed compounds. Those trials are described in the attached scientific publications and news articles (See Appendix H). These publications and articles demonstrate that the claimed compounds are effective in the in vivo treatment of both HIV and hepatitis B virus infections.

VIII. Conclusion

For the foregoing reasons, the Examiner's Final Rejection of claims 3-5, 7, 10, 21 and 22 under 35 U.S.C. §§ 102 and 103 is in error. Accordingly those rejections should be reversed and claims 3-5, 7, 10, 21 and 22 allowed.

Respectfully submitted,

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